Remarks

I. Claim Amendments

Claims 3-8, 12-16 and 19 are currently pending. Claims 3 and 5-8 have been amended to clarify that the moiety from which the α-amino is cleaved in step a) is either the amino acid attached to the support or the peptide attached to the support. Claim 19 is amended to clarify that the steps being referred to are the steps of claim 16, not the steps of claim 3. No change in the scope of the claims is intended by these amendments, and no new matter has been added.

The withdrawal of the previous grounds of rejection under 35 USC 112 second paragraph, 35 USC 102(b) based on Hudson, and 35 USC 103 based on Mihala and Thaler, is noted with appreciation.

The withdrawal of claim 15 from consideration is respectfully traversed, as discussed in greater detail below.

II. Response to Claim Rejections

A. Claim Rejections, §112, second paragraph

Claim 19, which depends from claim 16, stands rejected as being indefinite, the Examiner stating that it is unclear whether "step a) and step b)" as referred to therein are intended to indicate steps a) and b) of claim 16, or steps a and b of claim 3, which is referred to in step b) of claim 16. The ground of rejection is well taken, and claim 19 accordingly is amended herein to clarify that the steps being referred to are the steps of claim 16. It is respectfully submitted that this amendment is sufficient to overcome this ground of rejection.

B. Claim Rejections §102(b)

i. Birr

The rejection of claims 3-5, 14, 16, and 19 as anticipated by Birr is respectfully traversed. It is submitted that the rejection may be based on a misreading of the claims. The action states at page 6, lines 3-8,

> "Although applicants argue that Birr does not teach the use of a salt in steps a, b, or c of the instant claims, claim 3a refers to cleaving the alpha-amino protecting group OR the peptide attached to the support. [emphasis in the original] Thus claim 3a refers to cleaving either the alpha-amino protecting group or the peptide itself. The use of the word 'or' is evidence of alternate elements being cleaved. In the instant case, Birr expressly teach cleaving the peptide that is attached to the support (column 7 lines 34-36) as recited in the instant claim."

Prior to the amendment herein, claim step 3a recited "cleaving the α-amino protecting group from the amino acid or peptide attached to the support." It is apparent from the comment in the Action that the Examiner was reading this clause as *either* cleaving the alpha-amino group from the acid *or* cleaving the peptide from the support. In fact, it is the alpha amino group that is being cleaved, and it can be cleaved either from the amino acid, or from the peptide, either of which are attached to the support, as explained in the preamble. In other words, the word "or" relates to the word "from," not the word "cleaving." All the claims that include this same language have been amended to clarify that the alpha amino group is cleaved from either the amino acid that is attached to the support or from the peptide that is attached to the support. These amendments do not change the scope of the claims, other than to remove an apparent ambiguity. As step a) of the claims no longer can be interpreted as reciting cleaving the peptide from the support, it is respectfully submitted that this ground of rejection is overcome.

ii. Merrifield as evidenced by Finger

The rejection of claims 3-4, 7, 14, 16, and 19 as anticipated by Merrifield as evidenced by Finger is respectfully traversed.

It is acknowledged that Finger teaches that "Triton B," the use of which is discussed in Merrifield, is benzyltrimethylammonium hydroxide.

It is submitted however, that Merrifield does not anticipate the present claims. The preamble of claim 3 recites that the process is conducted on an "...amino acid or peptide which is protected by an α- amino protecting group and which is attached to a support...." Step a) of the claims recites "cleaving the α-amino protecting group" on the amino acid or peptide. In the various procedures disclosed in Merrifield, there are no procedures in which the peptides attached to a resin support are provided with an α-amino protecting group which is then removed before another amino acid is added, as recited in the preamble and step a) of the claims. In Merrifield, the α-amino protecting group is only on the amino acid that is to be added to the peptide.

The particular portions of Merrifield cited in the Action do not meet the limitations of the claims herein. The Action states at page 6 that "Merrifield teach (page 1293 section 'acylation') that a resin bound peptide prepared by solid phase synthesis was reacted with Boc-Ala in the

presence of Triton B." In fact, the cited portion of the reference states, "When a strong base such as Triton B was used to deprotonate the amidinopeptide resins, acylation became possible with a DCC-activated Boc-amino acid or with a preformed symmetrical anhydride. Thus, HCl·Dca-Gly-Val-Res gave 63% of Ala-Dca-Gly-Val-Res. (page 1293, right-hand column)" First, HCl·Dca-Gly-Val-Res does not include an α-amino protecting group, and there is no teaching of cleaving such an α-amino protecting group. In fact, Dca (N,N′-dicyclohexylamidino) is a guanidino group (formula III on page 1291) which is formed as a side reaction between a diimide, like DCC, and a free amino group (formula I and II on page 1291). The product thus obtained by Merrifield is the amidinopeptide resin (Dca-peptide resin) which easily forms the guanidinium salt with acid (e.g. HCl · Dca-peptide resin). A weak base like DIEA is not capable of deprotonating the N-terminal guanidinium group, in contrast to a strong base like Triton B (abstract on page 1291 and on page 1291, right hand-column). After treatment with Triton B, the formed guanidino group reacts with the α-carboxy group of a Boc-amino acid. The product thus obtained (Ala-Dca-Gly-Val-Res) partly consists of amino acid residues (-Ala- and -Gly-Val-) and partly of a non-amino acid residue (-Dca-). Thus, Merrifield does not state that the reaction with Boc-Ala was "in the presence of" Triton B, only that the amidinopeptide was first deprotonated with Triton B, then acylated. These reactions were conducted as separate steps (see page 1294, right-hand column, Section C). Further, the cited portion of the reference does not disclose that any wash steps were performed, as recited in step b) of the claims.

The Action further states at page 6 that "Merrifield teach (page 1294 section 'acylation of amidino peptide resins') that the product was cleaved from the resin and identified using chromatography." The cited portion of the reference includes three subparagraphs A, B, and C. It is believed that the Action is referring to Subparagraph B, which states that a resin containing HCl·Gly-Val-Res and HCl·Dca-Gly-Val-Res was washed with DIEA and treated with Boc-Leu and DCC. Leu-Ala-Gly-Val was identified chromatographically following cleavage from the resin with HF. This subparagraph does not disclose the use of Triton B, or any wash steps. Subparagraph C recites a different procedure in which Triton B was used, but does not recite any wash steps. If wash steps were used in this procedure they would have been recited, as such wash steps were recited in the other experimental procedures described on page 1294, in column 1 at lines 29, 42, 44, and in column 2 at lines 5, 17, 30, 39, 44 and 75.

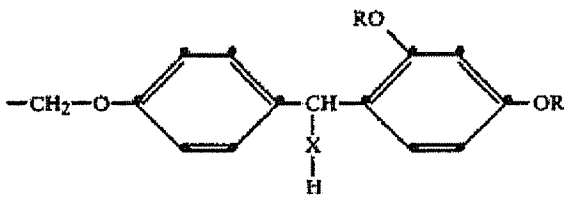
The statement "Since Merrifield teach solid-state peptide synthesis steps a-c of claims 3,7 are carried out" (Action page 7) is respectfully traversed. The mere fact that Merrifield teaches a specific embodiment of solid-state peptide synthesis does not mean that it meets the limitations of the present claims. In particular, Merrifield investigated a side reaction between a peptidyl resin and the diimide coupling reagent DCC. Taking claim 3 as representative, the preamble recites that the amino acid or peptide that is bonded to the support has an α-amino protecting group. The peptide chains bonded to the resin supports in Merrifield have no such α-amino protecting group but instead have the unwanted, permanent guanidinium group (HCl · Dca-peptide resin) formed after this side reaction. Thus, there is no step in Merrifield of cleaving the α-amino protecting group, as recited in claim 3 step a), so that the now unprotected N-terminus can bind to another amino acid. To the contrary, the unwanted guanidinium group can bind to another amino acid (Ala-Dca-peptide resin). Claim 3 step b) recites thorough washing. Although Merrifield discloses some procedures in which washing is used, it does not disclose washing as being used in any procedure involving Triton B.

For the reasons stated above, it is respectfully submitted that Merrifield does not anticipate the claims as amended, and it is requested that this ground of rejection be withdrawn.

C. Claim Rejections §103(a) – Rink, Mihala, Merrifield, and Finger

The rejection of claims 3-8, 12-14, 16 and 19 as obvious under this combination of references is respectfully traversed.

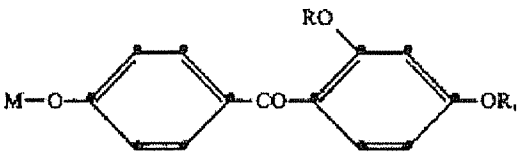
Rink (U.S. 5,004,781) discloses a resin suitable for use in a Merrifield solid-state peptide synthesis, and a method for making the resin. (Note that the 1962 Merrifield reference cited in Rink at col. 1, lines 43-44 is not the 1977 Merrifield reference cited in the present Office Action.) The resin of Rink is characterized (col. 1, lines 16-28) in that it has been substituted at benzene rings of its skeletal structure by groups of the formula



in which X represents –O- or –NH- and R represents C_1-C_4 alkyl.

In the method of making the resin, a suitable polystyrene is reacted, in succession,

(a) with a compound of formula



(II)

in which M is an alkali metal and R has the meaning given above,
(b) with a reducing agent and, if X represents —NH—,
(c) with a reagent that introduces the amino group.

(Rink, col. 3, lines 36-53) In process step (b) of Rink, the oxo group of formula II is converted to a hydroxyl group (col. 4, lines 10-13). If "X" in formula (I) is to be an –NH-, then the hydroxyl group is converted to an amino group (col. 4, lines 32-35). This can be done by use of ammonia gas (col. 4, lines 35-42) or carbamates (col. 4, lines 43-47). In the case of carbamates, the reaction is conducted by suspending the "hydroxyl resin" in an inert organic solvent and stirring with a strong organic acid (col. 4, line 57 – col. 5, line 2.) "In this manner a synthetic resin of the above-defined structure is obtained that carries instead of the –X-H group a –NH-W group in which W represents an amino-protecting group that can be removed by treatment with a base..." (col. 5, lines 2-6) or with "...an alkali metal hydroxide, for example sodium hydroxide, or an ammonium hydroxide, for example benzyltrimethylammonium hydroxide..." (col. 5, lines 19-22).

It may be seen that this portion of Rink, cited at page 9 of the Office Action, relates to a method of making a support resin, **not** to a procedure for conducting a Merrifield solid-state peptide synthesis. The cited portion of the Rink patent does not pertain to the subject matter of the present claims.

Mihala teaches a solid phase peptide fragment condensation protocol in which the coupling step (step c of representative claim 3 herein) is conducted in a 3:1 chloroform-phenol solvent system with a combination of 3-hydroxy-3,4-dihydro-4-oxo-1,2,3-benzotriazine (HODhbt) and its tetrabutylammonium (TBA) salt as additive. (Abstract) The TBA*ODhbt salt of Mihala is not one of the salts recited in claim 3. Moreover, claim 3 specifically recites that if

the salt is added in step c, then the solvent system is not to be chloroform-phenol. Mihala therefore teaches **away** from the invention as presently claimed.

Further, the effect of the added salt in the present invention is totally different from the effect in the Mihala reference. In Mihala, DIC is used as a coupling agent and HODHbt is used as a coupling additive. It is commonly known that during amide formation, first the unprotected C-terminus of the α-amino protected amino acid or peptide adds to the carbodiimide group of DIC thus forming the O-acylisourea which in turn reacts with HODHbt to form the C-terminally activated (as -CO-ODHbt ester), α-amino protected amino acid or peptide which finally couples to the amino acid or peptide (H_2N-) under formation of the amide bond (-CO-NH-) (see, Bodanszky, Peptide Chemistry, A Practical Textbook, Springer Verlag, 2nd edition, pages 63-66, submitted herewith as Exhibit A). HODhbt is therefore the starting material for the activated α-amino protected amino acid or peptide which is the acylating agent during the amide formation. Mihala et al found that HODhbt was not properly dissolved in chloroform-phenol or chloroform-TFE solvent systems. Mihala enhanced the solubility of this reagent by applying its salt form (TBA · ODhbt) (page 567, left-hand side, first two paragraphs) thereby enhancing the coupling efficiency (page 567, right-hand side, last paragraph) as well.

In contrast, the specific salts according to the pending claims are not used for enhancing the coupling efficiency - by enhancing the solubility of one of its coupling reagents - but to improve the elimination of excess of amino acids or cleavage reagents (specification, page 9, lines 32-35).

Contrary to the action (page 10) Rink and Mihala taken together do not teach peptide synthesis and the use of ammonium salts during the process. As noted, Rink only teaches the use of a salt in one embodiment of a method of making a resin, not a method of peptide synthesis; thus Rink does **not** "teach a salt as recited in the instant claims" (Office Action page 11). Mihala does not teach any of the salts recited in the present claims, and teaches a solvent system expressly excluded from the present claims. Merrifield does not make up for these deficiencies, for the reasons stated above.

Therefore, in view of the foregoing and in light of the clarifying amendments to the claims presented herein, Applicants believe that this rejection has been overcome.

III. Rejoinder of Claim 15

In the Office Action of July 24, 2008, the Office required elections of species with respect to the salt and the alpha amino protecting group. The action stated, "Upon allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of the allowed generic claim as provided by 37 CFR 1.141." In the present case, all of the independent claims have been shown to be allowable over the cited art of record. Previously withdrawn claim 15, which depends from allowable claim 3 and includes all the limitations thereof, is now entitled to consideration, as stated in the original Action. It is respectfully requested that claim 15 be rejoined in the case.

Conclusion

Applicants submit that the rejections proffered by the Office have been overcome, and that the Application is now in condition for allowance. The Applicants invite the Examiner to contact the undersigned as indicated below if the Examiner believes that this would expedite prosecution of this application.

Respectfully submitted,

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